HERITABLE DISORDERS OF CONNECTIVE TISSUE

V. OSTEOGENESIS IMPERFECTA

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HISTORICAL NOTE

SCATTERED reports of this disorder date back at least to 1678.[101] In the early descriptions the disease was usually ascribed to maternal impression. It was said, for instance, that the mothers, while pregnant, saw criminals broken on the wheel or witnessed severe bone-breaking accidents. In 1788 Ekman devoted his thesis at Upsala to the description of this disease in members of four generations in one kinship and presented strong evidence of its inheritance as a dominant. (See Seedorff[101] for an extensive translation of Ekman's original Latin thesis.) Lobstein[75] (1777-1838), gynecologist and pathologist of Strasbourg, wrote on the adult form of this disease in his textbook of morbid anatomy (1833); and Vrolik[121] (1801-1863), Dutch anatomist, described the disease in the newborn infant. Ormerod[88] was early to describe a case in 1859. In 1896 Spurway[107] noted the association of blue sclerotics. In 1900 Eddowes[40] extended this observation and made the significant suggestion that this disease is a "hypoplasia mesenchymialis," a theory for which Bauer,[11-13] Key,[72] and others, including notably and most recently Follis,[45-47] have provided supporting evidence. In 1912 Adair-Dighton[1] mentioned deafness in affected persons, and van der Hoeve and de Kleijn[118] in 1918 clinched this as a bona fide feature of the syndrome.

The terms which have been applied to this syndrome are numerous and include, to mention a few, osteogenesis imperfecta (Vrolik[121]), mollities ossium (Ormerod[88]), fragilitas ossium (Gurlt[58]), and osteopsathyrosis idiopathica (Lobstein[75]). To complicate matters further, the disease is called *la maladie de Lobstein* in the French-speaking portion of the medical world; Eddowes' syndrome (brittle bones and blue sclerae); van der Hoeve's syndrome (brittle bones, blue sclerotics and deafness) and Vrolik's disease (osteogenesis imperfecta congenita).

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Looser[76] suggested the terms osteogenesis imperfecta congenita (OIC) and osteogenesis imperfecta tarda (OIT).

CLINICAL MANIFESTATIONS

Over 50 kinships with at least one affected member have been identified in the records of this hospital, the Children's Hospital School, and the Kernan Hospital for Crippled Children.

The clinical aspects of osteogenesis imperfecta will be discussed under the headings of skeletal, ocular, cutaneous, otologic, and internal. The osseous manifestations greatly outweigh the others in significance.

Clinically two varieties of OI have been distinguished. In so-called osteogenesis imperfecta congenita, the disease is so severe that the relatively minor traumata to which the fetus is exposed in utero produce numerous fractures. The victim is usually born dead or survives only a short time. In the second variety, so-called osteogenesis imperfecta tarda (or tardiva), the manifestations are so mild that blue sclerae may be the only manifestation and fractures may occur only late in life or not at all. (Seedorff[101] further divides osteogenesis imperfecta tarda into levis and gravis types. In the latter, the first fractures are likely to occur when the patient is an infant. In the former, the fractures occur only considerably later.)

The above are artificial distinctions based only on the particularly wide variability of clinical expression in this disorder of connective tissue. OI congenita and OI tarda are fundamentally one and the same disease, the only basis for distinction being that the cases in the two groups are at opposite ends of the bell-shaped curve of expressivity. The foundation for this statement lies in the facts (1) that the two varieties of the disease sometimes occur in different members of the same family; (2) that there is a continuous spectrum of expressivity through the two major varieties; and (3) that the histologic anatomy of the two varieties is qualitatively identical.

On the basis mainly of radiologic changes, Fairbanks[44] distinguishes a "thick bone type", a "slender bone type," and a form he calls osteogenesis imperfecta cystica (Fig. 8,*B*). These, like the antenatal and postnatal distinction which he makes, probably have no basis as far as difference in the fundamental defect is concerned. During prepubertal years a patient may demonstrate an evolution from the "slender bone type" to the cystic type or the "thick bone type."

In summary, *all the several clinical pictures which are referred to in this communication, and which go by separate names in many instances, are one and the same disease which has wide systemic manifestations and an exceedingly great range of clinical severity (expressivity).*

The Musculoskeletal System[20].—As will be seen later, osteogenesis imperfecta is an hereditary defect of bone matrix. Calcification of what bone matrix is formed probably proceeds normally. Osteogenesis imperfecta is then a form of hereditary osteoporosis inasmuch as osteoporosis is defined as a deficiency in the formation (or an acceleration of the breakdown) of bone matrix. This is an important consideration in the understanding of some of the clinical manifestations of the disease and in its rational therapy. For example, in later life,

particularly if few fractures have occurred, the disease may masquerade as postmenopausal osteoporosis; immobilization is as bad for OI as it is for other forms of osteoporosis.

Caput membranaceum and micromelia ("tiny extremities") are the characteristics of OIC (Figs. 3 and 4). The limbs are described as bowed on the chest and abdomen at birth. If the patient survives, the bowing is likely to persist. Chondrodystrophia fetalis (achondroplasia) is often misdiagnosed. By x-ray (see Fig. 4) the skull is likely to show a mosaic pattern in the occipital area as a result of the presence of numerous Wormian bones.[96] This mosaic phenomenon was very striking in the case described and illustrated by Vrolik in 1849[121] (see Plate E of ref. 16). (This was the first case to which the name osteogenesis imperfecta was given.) Caffey states that the mosaic phenomenon occurs in only two conditions: osteogenesis imperfecta and cleidocranial dysostosis (see Fig. 43 of ref. 28 and compare with Fig. 4 here). The diagnosis of OIC has been made at times in utero by means of x-ray.[38] In this form, OI is a lethal or sublethal trait. Death is usually the result of intracranial hemorrhage and other injury since the calvarium offers little protection during delivery and later.

In OIT, the triviality of the trauma which may cause fracture is well known: fracture of the forearm in whittling or throwing a chip, of the phalanges in writing, of the femora when another person sits on the patient's lap[109] or when the patient stretches out in bed. Apert[6] called these patients "les hommes de verre." Sudden muscle pulls may fracture bones: the olecranon, for instance, has been pulled off by the triceps muscle in swimming[1] or even less strenuous exercise. Relatively little pain tends to accompany the fracture, due probably to the facts that there is minimal soft tissue trauma and that the patients become accustomed to the frequent fractures. Occasionally they learn to set their own fractures.[122] The fractures appear to heal with normal speed but occasionally the callus is so large (see Fig. 8,*A*) as to suggest osteosarcoma.[1,44,73,101,113] However, unlike Paget's disease, malignant degeneration is not recognized as a definite complication of this disease although bone neoplasms have been described.[68,128] Patients (e.g., J. B., in Fig. 6) are sometimes operated on for suspected osteosarcoma. At times overgrowth of bone occurs without evident fracture, and exostosis-like abnormalities develop. (Wide hypertrophic scars occur at the sites of surgical operations such as laparotomy.[97] These may be fundamentally analogous to the hypertrophic callus formation.) Functionally awkward pseudoarthroses may develop. The development of numerous Wormian bones in the occipital area of the skull[96] is a similar phenomenon seen particularly in the "congenital" form of the disease. In the series studied at this hospital, one cannot corroborate, in adults at least, the impression[10] that fracture of the neck of the femur is uncommon as compared with other types of osteoporosis. There is no sex difference in the severity of the fragilitas ossium.

By x-ray all bones have thin cortices and the long bones usually have a slender shaft with rather abrupt widening as the epiphysis is approached. There are instances, as Fairbanks[43,44] has indicated, in which the shaft of the long bones is thick, and yet others in which a cystic appearance is presented on x-ray (Fig. 8). Calcification of what matrix is present is normal.

As in other types of osteoporosis, "codfish" or "hourglass" vertebrae develop as a result of the biconcave deformity produced by the pressure of the normally elastic nucleus pulposus on the abnormally soft bone of the vertebral body (Fig. 7). Furthermore, "schmorlsches Knötchen," actual herniations of the nucleus pulposus into the substance of the vertebral body, may occur. (Schmorl's nodes derive their eponym from G. Schmorl who also did a classical study of Paget's disease of bone [see Section VIII of this series]).

Characteristically the adults have short legs as compared with the upper part of the body. The shortness of the lower extremities is due in part to bowing and to fractures in the shafts of the long bones, but is also due in considerable degree to interference with growth by multiple microfractures at the epiphyseal

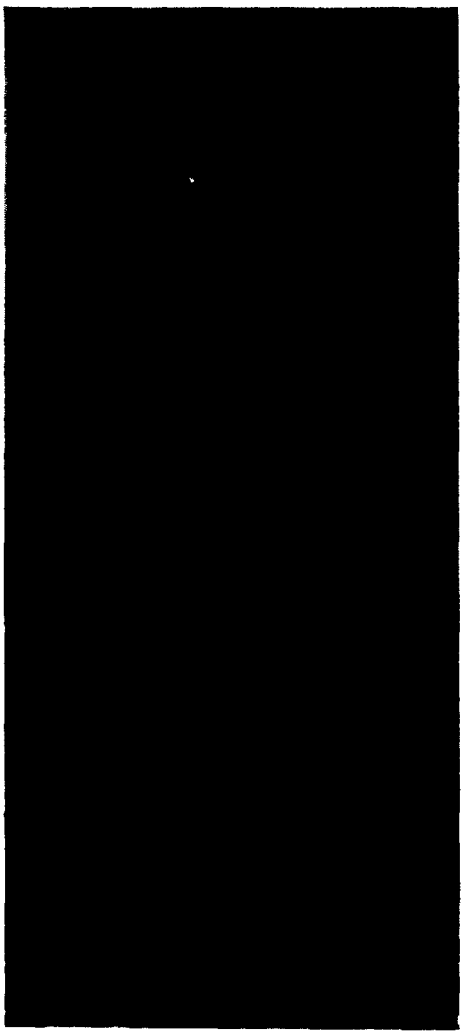


Fig. 1.—Seedorff[101] appears to have been responsible for first suggesting that Lautrec had osteogenesis imperfecta. All known facts and photographs such as this are consistent with the diagnosis.

ends of the bones. The short legs with trunk of normal size is unforgettably illustrated by Henri de Toulouse-Lautrec (1864-1901), French painter (Fig. 1). To play Lautrec in the motion picture *Le Moulin Rouge*, José Ferrer walked about on his knees. Marked bowing of the legs often results in a scissors-gait. By x-ray the femurs often assume a shepherd's crook appearance.

Gross deformities, which resemble somewhat those of Marfan's syndrome, such as kyphoscoliosis, koilosternia (pectus excavatum), and pigeon breast, are not uncommon. Arachnodactyly also has been described by several writers.[41,71,90,101] It must be remembered that arachnodactyly is a symptom, not a disease; that its presence does not indicate the coexistence of Marfan's disease. Unequivocal, or at least less equivocal, manifestations of the latter disease, such as ectopia lentis and involvement of the aortic media, have, with rare exceptions,[15] not been reported with osteogenesis imperfecta.

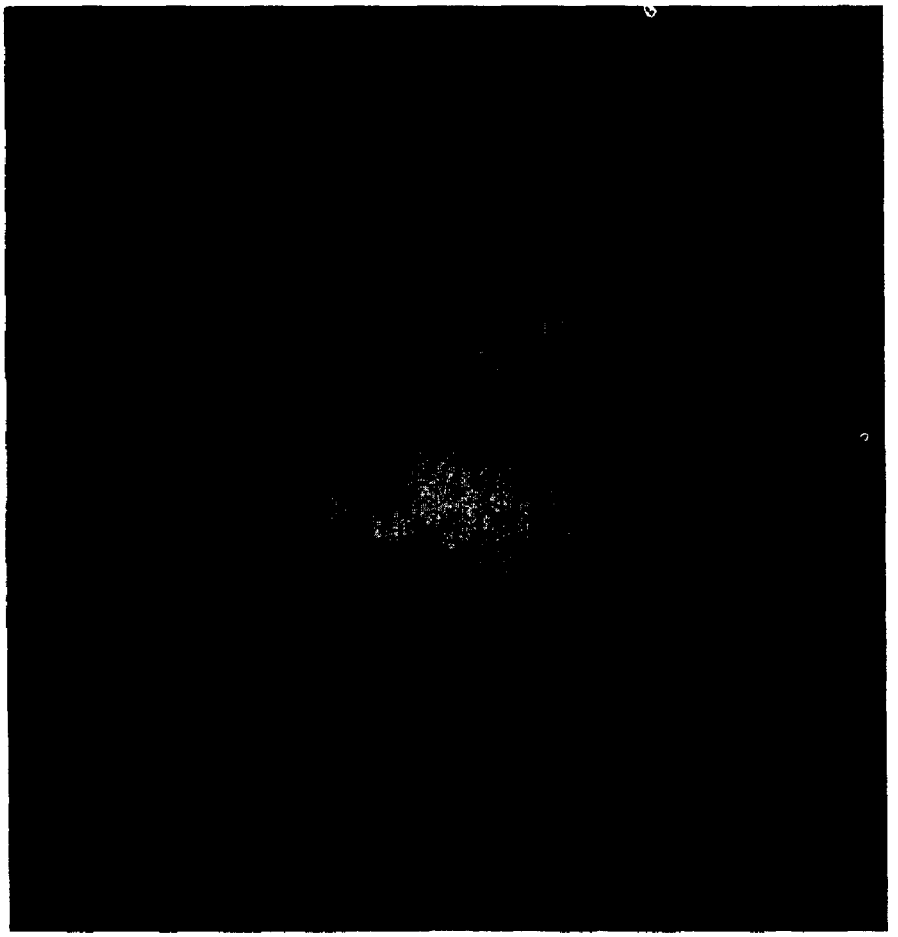


Fig. 2.—"Overhanging occiput" with decrease in the vertical dimension is demonstrated by the skull of this 51-year-old patient (G.I., 587372). She is edentulous. Definite platybasia was judged to be present. The patient has deeply blue sclerae and has had a large number of fractures dating from birth and resulting in marked deformity. She is scarcely taller than a 3-year-old child. Deafness of conduction type dates from the age of 13 years following pertussis and there has been intermittent tinnitus. She has had weakness of the left quadriceps muscle group, with absence of the left knee kick and anesthesia about the left knee, resulting presumably from a compression fracture of the lumbar spine.

The back is usually round and the thorax has a characteristic conical or beehive shape (see x-rays). The face is usually triangular due largely to the bulging calvarium and faciocranial disproportion. The forehead is broad and domed and the temporal areas are overhanging. The "temporal bulge"[37] and the "overhanging occiput"[41] (Fig. 2) are characteristic. The victims have trouble

getting hats large enough to fit them. As a result of the bulging calvarium, the ears tend to be displaced outward and to point downward. On skull x-ray the inferosuperior dimension is reduced. This, together with the "occipital overhang," the frontal bossing, and the platybasia which may be present in severe cases, results in a mushroom appearance of the skull on lateral x-ray. In general, as with so many other hereditary disorders, victims of this disease tend to resemble each other closely, even though they are quite unrelated. The facies and skeletal proportions are so characteristic that one can usually recognize the victims from a photograph, a feature useful in pedigree investigations.[101]

Fig. 3.—P.D. (A-42000), 3 months old, an instance of so-called osteogenesis imperfecta congenita. Micromelia is striking. The head appears disproportionately large. Numerous fractures were demonstrated immediately after birth. The patient was referred with the diagnosis of chondrodystrophia fetalis, however. The skull bones were described as "crumbly" on palpation. The parents and the parents' families were normal. By the age of 1 year there were evidences of well-advanced hydrocephalus. Death occurred at the age of 38 months.

Because of pelvic deformity, successful termination of pregnancy may be a serious problem.

By x-ray the bones are more radiolucent than normal. Bone age is proportionate to chronologic age.

The teeth are particularly susceptible to caries, are easily broken like the bones, hold fillings poorly, and, although normally shaped, may have an abnormal amber, yellowish-brown, or translucent bluish-gray coloration.[119] Both

deciduous and permanent teeth may show this peculiarity. The lamina dura, as in acquired types of osteoporosis, remains intact. The enamel is thought to be fundamentally normal[14] and the abnormality is thought to reside in the dentine. This prompted Roberts and Schour[91] to suggest the name *dentinogenesis imperfecta* for the dental aspect of this disease, rather than the terms *hereditary opalescent dentine* or *hereditary hypoplasia of the dentine*, which had been used before. Pedigrees in which this was presumably an isolated anomaly inherited as a dominant are described.[66,130] Some of these pedigrees are undoubtedly instances of the generalized disease, osteogenesis imperfecta, in which the dental manifestations dominate overwhelmingly. Roberts and Schour[91] were able to trace a family back five generations to 1763. The dental abnormality was very striking and was inherited as a strict dominant. Of forty-five individuals in five generations, twenty-two were affected. The authors made reference to other evidences of a mesenchymal defect.

The joints are characteristically excessively mobile[18,59,62,101] in this condition, just as in the Marfan syndrome and the Ehlers-Danlos syndrome. It is said[101] that this characteristic is at times so striking that the subject can perform as a contortionist. The basis is in part the presence of weak, stretched tendons and joint capsules and in part the deformity and maladaptation of the bony surfaces of the joints. Grossly, Key[72] described the Achilles tendon in one patient as "the diameter of a lead pencil (0.6 cm.) and translucent in appearance, there being a striking absence of the dense white fibrous tissue usually seen." From the standpoint of histology and of pathologic involvement in a number of diseases, the sclera bears many resemblances to tendon.[51]

Rupture of the inferior patellar tendon may follow exertion with more forceful quadriceps activity than usual.[78,109] Habitual dislocation of joints[9,15,25,64,111,115] or of the patella,[50] pes planus, and pseudoclubfoot[101] are frequent occurrences. The articular laxity probably exposes the victim to falls which are so likely to result in fracture.

Scoliosis may develop as a result of laxity of ligaments as well as of vertebral osteoporosis (Fig. 5). The spinal deformity is often extreme. Pain in the back is frequent in these patients. As in the Marfan syndrome, muscular hypotonia and underdevelopment has been emphasized by several writers.[7,8,35] As in the Marfan syndrome, these features are quite clearly secondary to the anomalies of the tendons and joints and to general debility with reduced muscular activity. The fibrous skeleton of the muscles may be defective, but there is no evidence that the muscle cell itself is at fault. At times, in children (N.T., A46910) enlargement and weakness of the limbs has suggested pseudohypertrophic muscular dystrophy.

Hernia occurs with high incidence in these patients (see Pedigree 603 in ref. 16), as with all the other hereditary connective tissue disorders under discussion, except pseudoxanthoma elasticum.

The Eye.—Blue sclerotics constitute the ocular hallmark of this syndrome. The color of the sclera is described at times as robin's egg blue, at times as slate blue. Of the manifestations of this disease, blue sclerotics are the most frequent.

Occasionally they are absent in unmistakable instances of the syndrome. This is not surprising since a high degree of variability in severity (expressivity) of this manifestation is to be expected, and overlap with the curve of normal distribution is likely to occur. Impressively blue sclerae are not infrequently encountered in persons free from all stigmata of this syndrome.

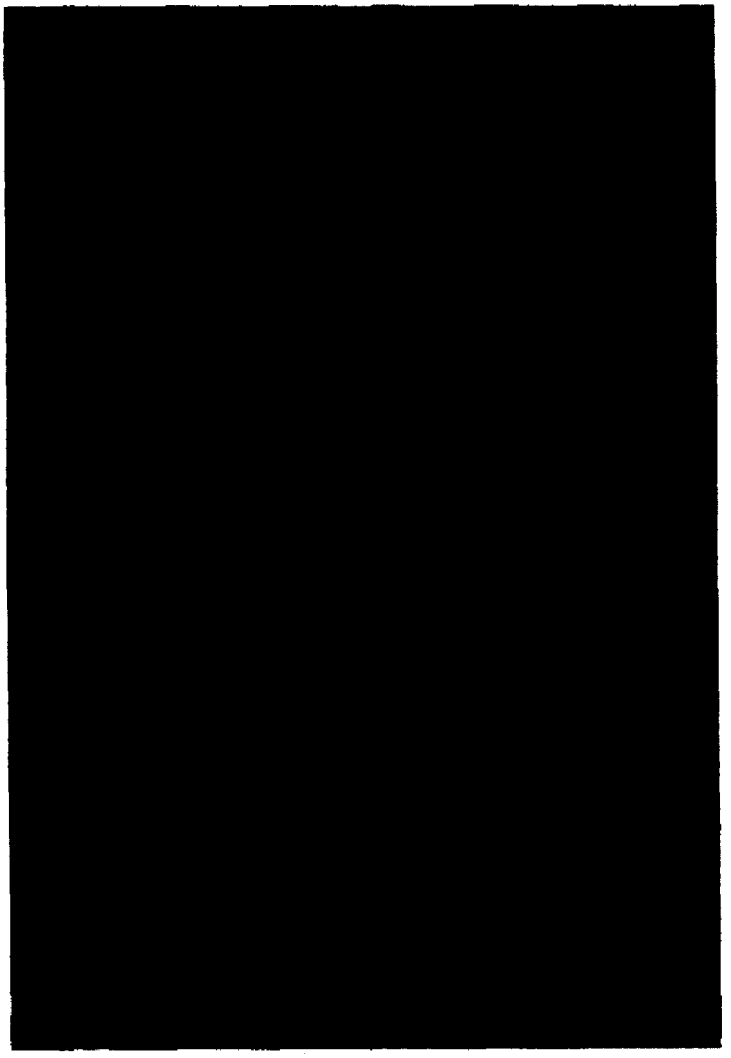
Embryotoxon, a congenital opacity in the periphery of the cornea sometimes called arcus juvenilis, is very frequent.[24,89,92,117,132] By slit lamp the cornea is measurably thinner than normal.[132] Hypermetropia appears to be significantly frequent.[1,2,36,111,112] Chorioretinitis, probably on an independently inherited basis, was reported by Colden.[83]

Other clinical manifestations probably closely related to the same defect of scleral connective tissue are keratoconus,[8,15,26,39] megalocornea,[39] maculae corneae.[120] Behr's patient[15] had ectopia lentis. Premature arcus senilis is described.[120] In two cases observed at this hospital[78] glaucoma has been present. In one it was discovered soon after birth (R.F., 194765) and has been termed congenital; in the other (H.J., 428403) the right eye was rendered blind (phthisis bulbi), presumably by glaucoma, at the age of about 20 years, and the other eye later was affected by so-called chronic, wide-angle glaucoma. There are a few reports of associated glaucoma in the literature.[115,129]

The Skin.—The skin in this condition is characteristically thin and translucent. It may resemble prematurely the atrophic skin of the aged. Healing of skin wounds has been found, by study of surgical incisions in these patients, to result in wider scars than usual.[97] Subcutaneous hemorrhages tend to occur after minor injuries[29] and tests of capillary fragility may be positive.[101] Macular atrophy of the skin is described by Blegvad and Haxthausen.[21] This may be comparable to the spotty blueness of the sclera in some instances.[120]

The Ear.[23,34]—Although the histologic patterns are distinct (v. seq.), the clinical[19,20,25,32,49,99,112,115,118] pattern of the deafness which accompanies this syndrome differs in no respect from that of otosclerosis. Stenvers[110] demonstrated that characteristic sclerosis of the petrous portion of the temporal bone can be detected radiologically even before the impairment of hearing has its onset; and, of course, these changes may be present but not so located as to cause deafness. Deafness may have its onset in the teens, often begins during pregnancy.[48,101] In Nager's patient,[88] hearing loss had its onset at the age of 9 years. As with otosclerosis of other origin, two types, a common stapes-ankylosing variety and a rarer cochlear type, have been described alone or in combination. Therefore, there may be either conduction or nerve type hearing loss. Fenestration operation has been performed in two patients with good results by Shambaugh[102] and in one with indifferent results by Watkyn-Thomas.[125] As with other types of otosclerosis, middle-ear infection aggravates the hearing loss; and deafness may begin in pregnancy. There has been described[110] an interesting blueness of the tympanic membrane, analogous to the blue sclerotics as far as indicating thinness of the structure is concerned. The patient may complain of almost constant tinnitus for long periods and of attacks of vertigo. Labyrinthine disease uncomplicated by deafness has been described.[52,120]

Internal Manifestations.—As for cardiovascular involvement, Sundberg[114] and Johansson[69] have described calcification of large peripheral arteries in victims of OIC. Lobeck,[74] Colden,[33] and Voorhoeve[120] described premature arteriosclerosis. Congenital heart disease was present in one patient.[120] Hass[61] described heart disease in several members of a kinship. From the descriptions of one of the members of that pedigree, rheumatic heart disease seems to have been present in that individual. In general, the heart disease was probably unrelated to the OI.



A.

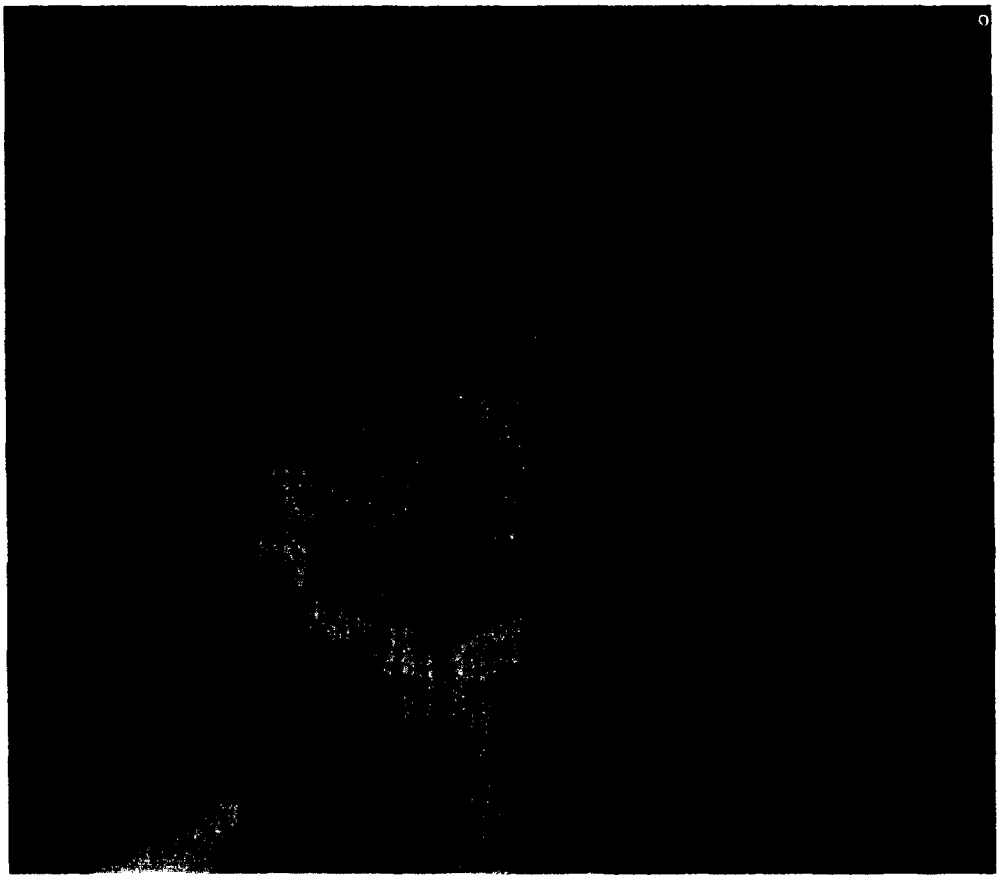
Fig. 4.—W. B. (A-79352), 2-month-old white male. Radiographic views (*A* and *B*) of the skull in a case of osteogenesis imperfecta congenita, showing a mosaic of Wormian bones and the thin calvarium characteristic of so-called *caput membranaceum*.

In one of my patients (J.G., 149692), with severe S-type rotary scoliosis (Fig. 5), a faint diastolic murmur has been heard to the left of the sternum and there is a borderline increase in systemic arterial pulse pressure. Whether this sound represents regurgitation at the aortic or the pulmonic valve or possibly has an extracardiac origin is unclear.

The severe spinal deformity may be followed by kyphoscoliotic cor pulmonale (e.g., C. B., 242806). Premature emphysema is frequent.

There are no pathognomonic chemical changes in the blood. Significant abnormalities of calcium and phosphorus do not occur. Alkaline phosphatase activity is often increased as a result of the multiple fractures.

Neurologic symptoms, particularly those of platybasia and of spinal cord compression, occur occasionally but are usually submerged by the other types of incapacitation from which these patients suffer. Backache and leg pains, which may have an element of nerve-root compression in their causation, are of frequent occurrence. Neurologic deficits attributable to this are less frequent.

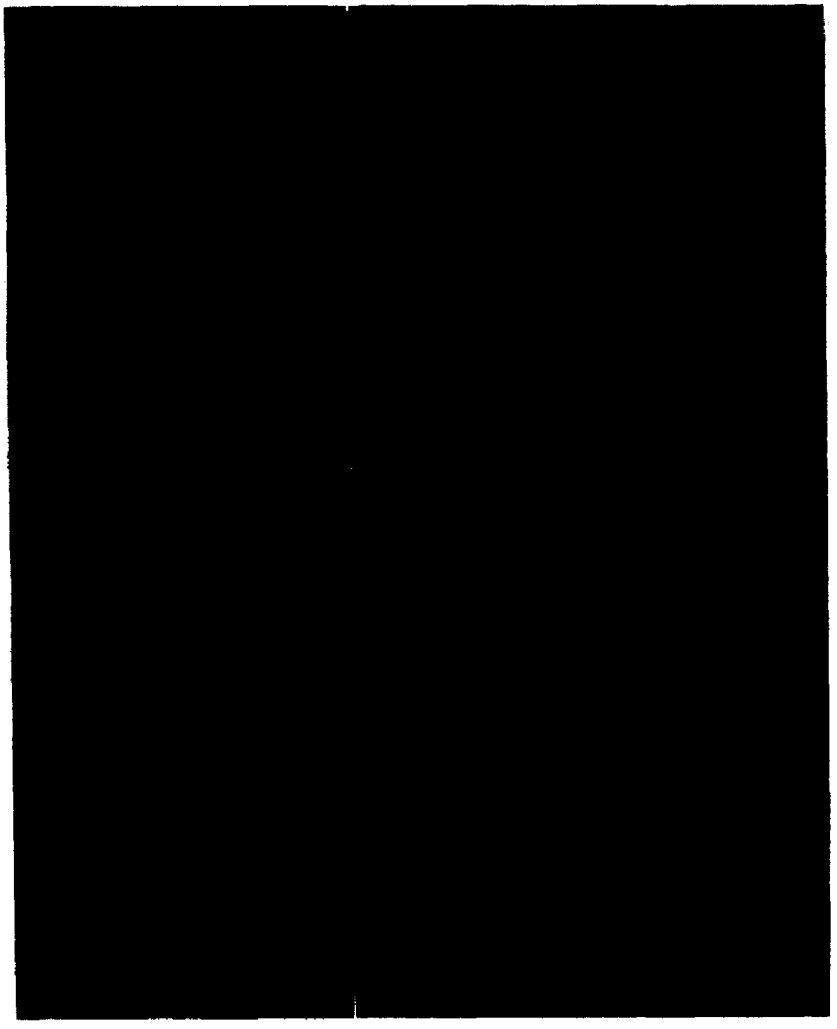


B.

Fig. 4, Cont'd. (*For legend see opposite page.*)

As with idiopathic varieties of platybasia (basilar impression), as well as that due to other bone-softening diseases such as Paget's disease, rickets, hyperparathyroidism, and sarcoid, four types of neurologic involvement should be sought[87]: (1) internal hydrocephalus; (2) bilateral, progressive cerebellar disturbance; (3) interference with the function of the lower cranial nerves; and (4) signs of spinal cord compression at the level of the foramen magnum. The impingement of the odontoid process of the axis on the brain stem is responsible for many of these manifestations.

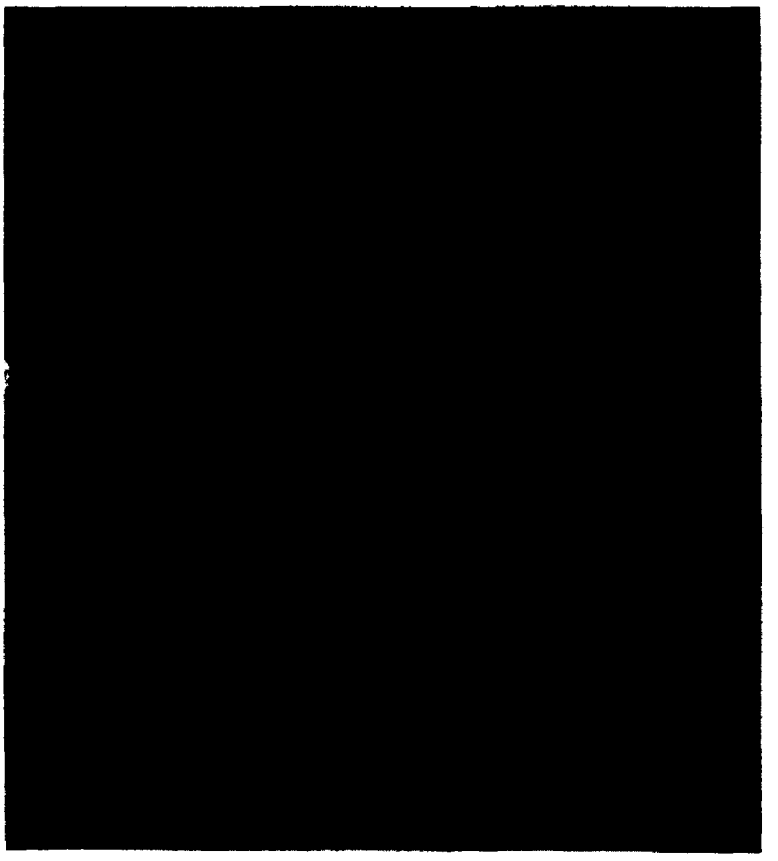
Two methods are used to detect platybasia radiologically: Chamberlain's line (from the posterior end of the hard palate to the posterior lip of the foramen magnum) normally lies above the entirety of the cervical spine.[30] Such is not the case in platybasia. According to Bull's index,[27] the plane of the axis is normally parallel to that of the hard palate, whereas, in platybasia, the two planes make an acute angle with each other. Plate F of Bell's monograph[16] shows the skeleton of a 12-year-old child with osteogenesis imperfecta and hydrocephalus. The photographs of the skeleton (preserved in the Museum of the Royal College of Surgeons) indicate fairly clearly that platybasia was present and may have been responsible for the hydrocephalus.



A. *B.*

Fig. 5.—J.G. (149692), 43 years old. In *A*, note the bulging calvarium with triangular facies. Flat feet and kyphoscoliosis are also evident in *A* and *B*. The x-ray in *C* reveals the complex spinal deformity present in this patient. The bones are more radiolucent than is normal. The sclerae are deeply blue. Deafness has been present since at least the age of 25 years and tinnitus has often been distressing. Scoliosis was first noted at the age of 13 years, and since the age of 16 years back pain has been a major complaint. The patient is, in general, loose-jointed with flat feet; the head of the humerus was dislocated on one occasion when she was thrown from a bicycle at the age of 7 years. A ganglion on the right wrist was described at one time. X-ray of the skull shows characteristic decrease in the vertical dimension. A diastolic murmur at the left sternal border remains unexplained. An amazing feature of this case of undoubted osteogenesis imperfecta is the fact that *no* fractures have occurred in spite of appreciable trauma on several occasions.

Summary of Clinical Manifestations.—Bell[16] provides entirely credible figures for the incidence of the several manifestations: among adult individuals "with blue sclerotics approximately 60 per cent have an associated liability to fracture, approximately 60 per cent have an associated otosclerosis, and 44 per cent suffer from all three defects." These values might be higher were it possible to eliminate those cases with hereditary blue sclerotics on some other basis. It has not been established that blue sclerotics can occur on an independent, genetically distinct basis and as an isolated anomaly. (They do occur with others of the hereditary disorders of connective tissue.) However, such seems likely from experience with similar situations.



C.

Fig. 5, Cont'd. *(For legend see opposite page.)*

INCIDENCE AND INHERITANCE

Among the five disorders under principal discussion in this series, osteogenesis imperfecta vies with the Marfan syndrome for first place as to incidence. It was relatively easy to accumulate fifty apparently unrelated propositi for purposes of this study.*

There is no peculiar racial distribution of OI, cases having been described in Jews[78] and American Negroes,[56,78,124] and in natives of Japan,[70,84] China,[31] India,[60] Egypt,[7,8] and Russia,[122] as well as all Western European countries.

*Patients from Baltimore or Maryland and patients who have been seen at some time at this hospital have been reported in several previous publications.[45,46,47,83,85,104]

The evidence is overwhelming that the disease is inherited as an autosomal dominant. Bell[16] found such to be the case for blue sclerotics in 73 kinships with a total of 463 affected persons. In an analysis of 89 families with 1,000 individuals of whom 515 were affected, Fuss[53] demonstrated autosomal dominance for the syndrome of bone fragility and blue sclerotics. One of the best-studied pedigrees is that of a family of the Eastern Shore of Maryland, reported by Hills and McLanahan.[63] Twenty-seven of 51 members of five generations were affected.

A. *B.*

Fig. 6.—J.B. (459707), 21 years old. Bowed deformities of the extremities, flat feet, moderately bulging skull are evident. As a result of the bulging skull, the ears point forward and downward. Beginning at the age of 8 years the patient has had a total of approximately thirteen fractures with no decrease in the incidence of these at puberty. The sclerae are deeply blue.

There is no evidence that osteogenesis can occur on any basis except that of mutation. Seedorff,[101] after studying 55 kinships with 180 affected individuals, constructed a complicated schema based on the theories (1) that each component of the syndrome is the result of a separate gene and (2) that three separate genes

A.

B.

Fig. 7.—Lateral views of the spine in two patients with codfish vertebrae. *A*, Patient J.L.L. (Children's Hosp. Sch.), aged 13 years. *B*, Patient H.R. (Children's Hosp. Sch.), aged 2 years.

control the bone fragility, mutation in one, two, or three being responsible, respectively, for OIT levis, OIT gravis, and OIC. This complex schema is untenable because of the arguments against a multiple gene basis of hereditary syndromes (see Section I of this series) and because of the probability on clinical and histopathologic grounds that the three arbitrarily designated states are in fact different grades of severity of the same disorder of connective tissue.

Frequently the statement appears that the so-called congenital form of the disease probably is not inherited in many instances or is inherited in a different manner (e.g., as a recessive) than the other forms. Many of such instances—severely affected stillborn children of normal parents—may be de novo mutations. I am not aware of the occurrence of two such offspring from parents who were indubitably normal. Even if the parents had to be considered normal by every gauge, suspicion of subtle abnormality would remain. When a severely affected offspring from very midly affected parents is encountered, there is the possibility that both parents are heterozygous and the child homozygous.

Even with the excellent system for indexing hereditary diseases in Denmark, Seedorff[101] concluded that one is not justified in attempting to calculate the mutation rate for this anomaly. Furthermore, Seedorff could find no conclusive evidence that the parents of patients with osteogenesis imperfecta tend to be older, as seems to be the case in chondrodystrophic dwarfism.[82] In his group of cases of OIT, Seedorff[101] concluded that these individuals are 1.4 times more productive of children than their normal siblings. As far as perpetuating the disease is concerned, each affected individual produced, on the average, 0.75 affected children. If it were not for constantly occurring new cases on the basis of mutation, the disease would in time disappear.

Bell[16] found, in tabulating reported cases of bone fragility with blue sclerotics on the one hand, and cases of bone fragility alone, on the other, a seemingly highly significant difference in sex incidence and mode of inheritance (whether through mother or father) in the two groups. Although the explanation for a basis, if such was the case, is not apparent, the use of published data rather than those accumulated in a uniform manner by the researcher himself is beset with such pitfalls that it is doubtful that one is justified in concluding, and Bell does not so conclude, that a fundamental difference is involved. On the basis of other experience, it is entirely likely that blue sclerotics and fragilitas ossium of otherwise indistinguishable character can occur as isolated, heritable anomalies genetically distinct from osteogenesis imperfecta. It is, of course, well-known that otosclerosis clinically identical with that of osteogenesis imperfecta occurs even more commonly as an isolated anomaly than as part of this syndrome. This is a situation somewhat comparable to that involved in the ectopia lentis of the Marfan syndrome: the manifestations may occur alone or as part of a complex syndrome.

Consanguinity is not impressively frequent in the pedigrees of OI. In the motion picture *Moulin Rouge*, the screen biography of Toulouse-Lautrec, the country physician, recognizing the boy's malady as one which is frequently hereditary, points out to the parents that they are first cousins and advises their separation. Actually it is likely that the consanguinity had nothing to do with

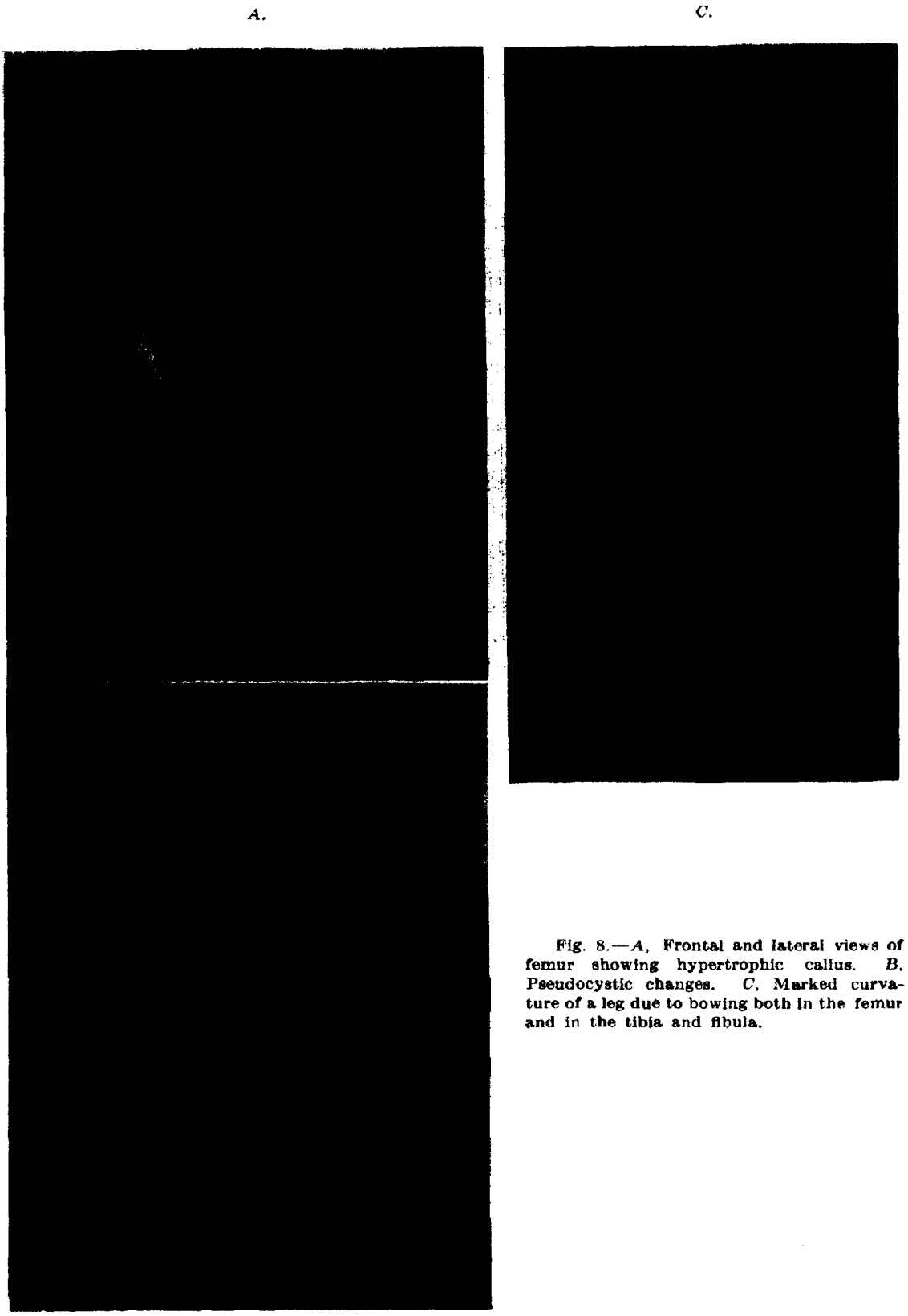


Fig. 8.—*A*, Frontal and lateral views of femur showing hypertrophic callus. *B*, Pseudocystic changes. *C*, Marked curvature of a leg due to bowing both in the femur and in the tibia and fibula.

the son's condition unless both parents carried the disease in very mild form so that there was a chance for the son to have the trait in "double dose," i.e., homozygous form. It is not known that either parent had any stigma of OI.

PATHOLOGY[67]

In the bones, a peculiar, basophilic, periodic-acid-and-Schiff-positive material has been found in place of osteoid. In other tissue, only argyrophilic reticulin fibers and no mature collagen are demonstrated. Histochemically, phosphatase activity is not demonstrably disturbed, epiphyseal cartilage appears to be completely normal,[46] and invasion of the regularly arranged cartilage cell columns by capillaries is normal. The metaphysis shows calcified cartilage but no true bone or osteoid. This calcified cartilage tends to fracture and fragment. Organic bone matrix fails to be deposited and in its stead a peculiar basophilic material makes its appearance. As stated above, the material stains with periodic acid and leucofuchsin and, furthermore, is argyrophilic. Follis[45] suggests that it may represent immature bone matrix in the manner that reticulin, which it resembles in its staining properties, may represent immature collagen.

Swedish workers using recently developed biophysical techniques demonstrated disorganization of the collagen matrix.[17,43] The specific techniques which they employed were microradiography, polarized light microscopy, and x-ray diffraction. Their findings are by no means inconsistent with those of Follis: ". . . in osteogenesis imperfecta the compact bone has a quite abnormal distribution of mineral salts and arrangement of organic fibers. . . . The immature fibrillar bone normally seen in the foetus and newborn infant resembles in several ways the tissue found in osteogenesis imperfecta. Normally this primary bone tissue is rapidly replaced by secondary bone after birth, but in osteogenesis imperfecta this secondary bone tissue is not found."

Osteoblasts and osteoclasts are usually present in normal numbers. Chemically, calcium and phosphorus are present in the bones in a normal ratio; the total content of bone salts is reduced, however.

In the skin, Follis[47] found absence of normal adult collagen fibers and substitution by argyrophilic fibers with other properties of reticulin. The shrinkage temperature of the skin was normal, however.

In the eye, decreased thickness of the sclera has been described as early as 1841 by v. Ammon[5] and more recently by Buchanan,[26] Casanovas,[29] and Follis,[46] but normal thickness was found by Bronson[25] and Voigt.[122] Ruedemann[95] has found histologic changes in cornea and sclera fundamentally identical to those described by Follis[46] in the corium. Clearly, the blue coloration is the result of the brown-pigmented choroid showing through the thin sclera.[127]

In sections of the teeth, "clod-like" calcification of quite abnormal type is seen. Rushton[94] showed that peripheral pulp cells produce "precollagenous" argyrophilic fibers but that these are not converted into collagen except in the immediate vicinity of blood vessels. These observations are in complete agreement with those of Follis, in bone, skin, and sclera.

Histologically the changes in the ear in osteogenesis imperfecta are quite distinct from those of otosclerosis despite the close clinical similarities. Studies have been made by Ruttin,[98] Gimplinger,[55] and others.

THE FUNDAMENTAL DEFECT

A generalized mesenchymal defect has been assumed for several decades. The recent histologic investigations of Follis (described above) appear to indicate that the fundamental difficulty may be in the maturation of collagen beyond the reticulin fiber stage. (This assumes that one can subscribe without reservation to the view that reticulin fibers are immature collagen fibers.[77] Even if this is not the case, it can be stated that the collagen fibers in OI are abnormal and resemble reticulin fibers in many respects.) As far as the bones are concerned, the disease must be considered a disorder of osteoblastic activity. Normal chondroblastic activity is suggested by the fact that growth and development of cartilage are normal.

It has been claimed by Seedorff[101] that a condition in cattle called anosteoplasia congenita[65] is an identical disorder.

MISCELLANEOUS CONSIDERATIONS

In general, a decrease in the incidence of fractures is observed after puberty with, possibly, an increase in this incidence after the menopause. Both clinical experience in man[4] and experimental evidence from animals[54] indicate an important role of sex hormones in the normal formation of bone matrix. This hormonal influence may explain in large part the observations cited above; increased vigilance on the part of the patient may be in part responsible for the improvement after puberty.

Estrogens and testosterone are worthy of more extensive trial in these patients.[93] Certainly it is important to avoid the superimposition of postmenopausal osteoporosis on the osteoporosis of this heritable disease.[81] Nonmasculinizing forms of androgens[57] can be employed. Serum albumin, which seems to be a percursor for bone matrix, is beneficial when administered to patients with certain acquired varieties of osteoporosis.[3] It apparently has not been used in osteogenesis imperfecta. Strontium has also not been tested,[103] with the exception of one study[22] in which the author thought the results were favorable and rendered further study worth while. As one might expect, all manner of medications have been employed for this distressing and longstanding disorder, for example, thymus extract.[100] Furthermore, because of difficulties in evaluating results, the variable course of the disease, and wishful thinking on the part of physicians and patient, enthusiastic reports have at times been forthcoming.

Unless quite by accident some efficacious therapeutic measure is discovered, no definitive progress in the therapy of OI can be anticipated until the precise reason for the failure of normal development and/or maturation of collagen is understood. Only then can measures directed at correcting the specific deficit be devised. There is every reason to anticipate that the biochemical defect in

hereditary disorders such as this will be precisely defined in the future. Optimism in regard to possibilities of correcting or modifying the basic defect is justified.

As in acquired forms of osteoporosis it is highly important to avoid immobilization of the patient because of the further depletion of bone matrix occasioned thereby. It is doubtful that a high intake of calcium, phosphorus, and vitamin D are helpful, and the combination of these with immobilization may have dire effects: C. B. (J.H.H. 242806) developed large bladder stones and a Proteus infection of the urinary tract after immobilization for eleven weeks in a cast, and a "bone-building diet" which included several quarts of milk a day and added calcium and vitamin D. The pinning and plating of fractures have much to recommend them because they reduce the necessity for immobilization. Deformity has been corrected by intramedullary nailing.[79]

Osteotomies and related procedures of orthopedic surgery are employed to correct deformities.

Pregnancy is not to be encouraged because of the 50 per cent chance of the child being affected and because of adverse effects of the pregnant and parturient[85] states on the skeleton. Deafness from otosclerosis often begins or is aggravated during pregnancy. Because of the pelvic deformities of the disease, delivery may be mechanically very difficult. One patient[78] has fractured her coccyx with each of the deliveries.

Because of inactivity it is easy for victims of this disease to become obese. Obviously, this is to be avoided. In young patients, Froelich's syndrome is sometimes suspected without basis.

SUMMARY AND CONCLUSIONS

Osteogenesis imperfecta is a generalized disorder of connective tissue involving, in addition to bone, the skin, ligaments, tendons, fascia, sclera, and inner ear. Although the most frequent functionally important manifestations are brittle bones and deafness, blue sclerae are a dramatic feature, and thin skin, loose-jointedness, and hernia occur as manifestations of a single basic defect.

An exceptionally wide range of expressivity has resulted in the description of several different syndromes, all of which are but different expressions of a single type of connective tissue disorder. The disorder is inherited as a Mendelian dominant.

Studies to date are most consistent with the view that the basic defect is one which involves the maturation of the collagen fiber beyond the stage of the argyrophilic, reticulin fiber.

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